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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/998,058	Applicant(s) THREADGILL ET AL.	
	Examiner Amanda M. Shaw	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 7/12/2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,46-53 and 61-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27,46-53 and 61-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed July 12, 2006. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made non-final.

Claims 1-27, 46-53, and 61-75 are currently pending. Claims 1, 46, and 74 have been amended. Therefore Claims 1-27, 46-53, and 61-75 will be addressed herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27, 46-53, 60-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising (a) providing a renewable population of genetically diverse mice that can be regenerated wherein a plurality of the gentically diverse mice are heterozygous for a detectable polymoprhism; (b) mapping the genomes of mice within the renewable population of genetically diverse mice that display a particular body weight, and (c) identifying a genetic locus on chromosomes 4, 6, and 12 that modulates the body weight through the mapping step (b), does not reasonably provide enablement for a method of identifying any locus that

modulates any phenotype in any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn broadly to methods for identifying a genetic locus that modulates a phenotype, the method comprising: (a) providing a renewable population of genetically diverse individuals that can be regenerated wherein a plurality of the gentically diverse individuals are heterozygous for a detectable polymoprhism; (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, and (c) identifying a genetic locus that modulates the phenotype through the mapping step (b). The claims further require that the individual is an animal or plant, a mammal, a rodent, and a mouse. The claims also require that the recombinant inbred lines be derived from at least 3, 4, or 8 different non-recombinant parent lines. The claims also require that the phenotype be selected from a visible, physiological, behavioral, susceptibility, cellular or molecular phenotype. Some of the claims require that the phenotype be modulated by one or more non-

genetic factors (i.e. environmental conditions or drug resistance) in addition to genetic factors. The breathe of the claims as written broadly encompasses methods for identifying any genetic locus that modulates any phenotype.

Nature of the Invention

The claims are drawn to methods for identifying any genetic locus that modulates any phenotype The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches at page 5 that the present invention provides a method for identifying a genetic locus that modulates a phenotype using a renewable population of genetically diverse individuals. The genomes of individuals within the renewable population of genetically diverse individuals that display a phenotype are mapped, thereby identifying a genetic locus that modulates the phenotype. The present invention further provides a method for identifying an interaction between a genetic locus and a non-genetic factor, wherein the interaction modulates a phenotype.

The specification further provides an example on pages 26-29 in which recombinant inbred (RIX) hybrids are generated using a collection of 13 independent CXB recombinant inbred lines. The RIX hybrids and RI parents were then used to analyze body weight which a morphometric characteristic controlled by quantitative trait loci. Interval mapping and composite interval mapping of the loci linked to body weight were then analyzed using the Map Manager QTX program. A single suggestive locus

on chromosome 4 was detected among the RI parents. By contrast four significant loci were detected among the RIX hybrids. One of the four significant loci corresponded to the same chromosome 4 locus detected among the RI parents. Additional significant loci were located on chromosome 6 and 12. Next the mapping information can be used to determine candidate genes which control body weight.

Additionally the specification provides an example on pages 29 in which recombinant inbred (RIX) hybrids are generated using a collection of 13 independent CXB recombinant inbred lines. The RIX hybrids and RI parents were then used to analyze brain weight. Interval mapping and composite interval mapping of the loci linked to body weight were analyzed using the Map Manager QTX program. A single suggestive locus on chromosome 11 was detected among the RI parents. By contrast one suggestive locus on chromosome 5 and one significant locus on chromosome 11 was detected among the RIX hybrids. The chromosome 11 locus detected among the RIX hybrids corresponded to the same chromosome 11 locus detected among the RI parents. Next the mapping information can be used to determine candidate genes which brain weight. However the specification does not teach how or why brain weight is important for mice.

The specification fails to provide an example in which any other locus is identified which modulates any other phenotype. Additionally there is no support provided in the specification for the assumption that that the loci identified that is responsible for body weight and/or brain weight in mice will be the same loci that is linked to body weight and/or brain weight in other organisms (i.e. plants, other mammals, humans, etc...).

Further the specification does not teach an example wherein the phenotype is a visible, behavioral, susceptibility, cellular, or molecular phenotype. Also the specification does not teach any phenotype that is modulated by a non-genetic factor (i.e. environmental condition or drug exposure).

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying a genetic locus that modulates a phenotype is highly unpredictable. For example Belknap (Behavior Genetics 1996) teaches that RI strains have recently been shown to be a valuable tool for mapping loci associated with quantitative traits, particularly as part of two or multistep mapping strategies. However their proper use in QTL mapping requires an appreciation of error risk, which this paper has shown are considerable but not insurmountable concerns (Page 159).

Therefore it is highly unpredictable as to whether the method of the present invention can be used to identify any genetic locus that modulates any phenotype. Knowledge that this method can be used to link chromosomes 4, 6, and 12 with body weight or chromosomes 5 or 11 with brain weight does not allow one to conclude that the method can be used to link any genetic locus that modulates any phenotype. The specification does not teach any other genetic locus that has been linked to any other phenotype.

Additionally it is highly unpredictable as to whether the findings that chromosomes 4, 6, and 12 are linked to body weight or chromosomes 5 and 11 are linked to brain weight in mice can be extrapolated to other organisms. Knowledge that a locus modulates a phenotype in one organism (i.e. mice) does not allow one to

conclude that this locus will also modulate the same phenotype in other organisms (i.e. humans, plants, etc...). The specification also does not teach any other organisms in which chromosomes 4, 6, and 12 are linked to body weight in mice or chromosomes 5 and 11 are linked to brain weight. Thus the specification does not teach that this method can be used for mapping in a representative number of different organisms.

Further it is highly unpredictable as to whether the method of the present invention can be used to identify an interaction between a genetic locus and a non-genetic factor wherein the interaction modulates a phenotype since the specification does not provide any evidence of this. Without extensive knowledge of how the non-genetic factor alters the specific phenotype it is highly unpredictable whether or not the method of the present invention can be used to identify an interaction between a genetic locus and a non-genetic factor. The genus of non-genetic factors that are capable of affecting phenotypes is quite large and each factor affects each phenotype differently. Additionally the genus of phenotypes that are affected by non-genetic factors is quite large and each phenotype is affected differently. In absence of evidence to the contrary the specification does not teach that this method can be used for identifying an interaction between a genetic locus and a non-genetic factor.

Amount of Direction or Guidance Provided by the Specification:

The specification teaches a method for identifying a genetic locus that modulates a phenotype. The specification teaches that this can be done by creating (RIX) hybrids using a collection of 13 independent CXB recombinant inbred lines and then using the RIX hybrids and RI parents to analyze a particular phenotype. Interval mapping and

composite interval mapping of the loci linked to the phenotype can be determined using the Map Manager QTX program. However, such experimentation may involve extensive experimentation using a multitude of phenotypes in a variety of different organisms. Such random, trial by error experimentation is considered to be undue. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Working Examples:

The specification provides two working recombinant inbred (RIX) hybrids are generated using a collection of 13 independent CXB recombinant inbred lines. The RIX hybrids and RI parents were then used to analyze body weight and brain weight. Interval mapping and composite interval mapping of the loci linked to body weight and brain weight were determined using the Map Manager QTX program. The specification does not provide any other working examples in which other phenotypes are mapped. Also the specification does not provide any other working examples in which other organisms are used. Additionally the specification does not provide any other working examples in which an interaction between a genetic locus and a non-genetic factor identified wherein the non-genetic factor modulates a phenotype.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.''' *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he

scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

While the specification is enabled for a method for identifying genetic loci on chromosomes 4, 6, and 12 that modulate body weight in mice, the specification does not reasonably provide enablement for a method of identifying any locus that modulates any phenotype in any organism. The specification fails to provide an example in which any other locus that modulates any other phenotype is taught. Additionally there is no data provided in the specification that teaches that chromosomes 4, 6, and 12 also modulate body weight in other organisms. Further the specification does not teach an example wherein the phenotype is a visible, behavioral, susceptibility, cellular, or molecular phenotype. Also the specification does not teach any phenotype that is modulated by a non-genetic factor (i.e. environmental condition or drug exposure). Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27, 46-53, 60-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-27, 46-53, 60-75 are indefinite over the recitation of the phrase "a population of genetically diverse individuals". This phrase in considered unclear because "a population of genetically diverse individuals" is not clearly defined in the specification and there is no art recognized definition for this phrase.

Claims 8 and 9 are indefinite over the recitation of the phrases "less than about 500" and "less than about 100". The phrase "less than" typically indicates a maximum point. The phrase "less than" however, is contraverted by the term "about" which implies that values above and below 500 and 100 nucleotides are permitted. Further, the extent of variance permitted by "about" is unclear in this context. Since nucleotides are whole numbers, "about 500 or 100" cannot mean from 511 to 97.6 because nucleotides cannot be split in half. Therefore, it is also unclear if "about 500 and 100" simply includes 508 or if it also includes 1-508 as well. In Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (CAFC 1991), the CAFC stated, "The district court held claims 4 and 6 of the patent invalid because their specific activity limitation of "at least about 160,000" was indefinite". After review, the CAFC states "We therefore affirm the district court's determination on this issue." Thus, the CAFC found the phrase

"at least about" indefinite where the metes and bounds of the term were not defined in the specification.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10, 60, and 75 are rejected under 35 U.S.C. 102(a) as being anticipated by Howard et al (Mammalian Genome March 2000).

Regarding Claims 1-10 Howard et al teach a method comprising (a) providing a renewable population of genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. Specifically Howard et al teach that the recombinant inbred lines AXB and BXA (which are both homozygous) were both used to study a mouse mutation that causes altered mammary gland development. Backcross and intercross of the AXB and the BXA lines display both alterations in the number and placement of nipples. Approximately 25% of both the AXB and BXA intercrosses and approximately 50% of the female backcross mice observed the mutant phenotype. Howard et al also teach

that they are now mapping the ska gene in the AXB/BXA recombinant inbred strains of mice and in the back cross and intercross panels in order to make a high resolution map to isolate the ska locus.

5. Claims 1-10, 15, 19-27, 46-53, 64-73, and 75 remain rejected under 35 U.S.C. 102(b) as being anticipated by Diehl et al (PNAS 1997) for reasons set forth in the Office Action of February 10, 2006 and reiterated below.

Diehl et al teach a method for identifying multiple genetic loci for example, *Col2a1, Col1a1* and *Col3a1*(page 5235) that modulate the phenotype of facial clefting in mice. Diehl et al have performed a genome-wide search for loci contributing to susceptibility to teratogen-induced facial clefting in the mouse. AXB and BXA recombinant inbred(RI) lines derived from crosses between A/J and C57BL6/J strains were supplied by M. Nesbitt and the mice were then bred by intercrossing recombinant inbred lines and maintained in a colony at the University of Michigan(page 5232) as a renewable population of genetically diverse individuals. The reference teaches this study for identifying a genetic locus in the diploid mouse system wherein the inbred lines of the renewable population of genetically diverse individuals comprise less than about 100 strains, in one instance a BXD set of 26 RI lines is used (page 5234). Experiments were also performed using the AXB and BXA RI strains to evaluate both spontaneous and teratogen-induced clefting resulting in both visual and physiological phenotypes. The reference uses the extensive data on teratogen-induced clefting in the

AXB and BXA RI lines collected previously with a genome wide collection of marker typings for these RI lines to study the effects of genetic polymorphisms segregating in the renewable population (page 5232, left column). Diehl et al. teach the resulting molecular phenotype of their mouse mutants with clefting phenotypes to include for example, eight collagen genes including an altered expression of one, *Col3a1*, which is normally expressed in the embryonic palate. The reference also teaches the method for identifying multiple genetic loci further comprising identifying two or more genetic loci that modulate the phenotype of clefting as seen on the reference's page 5235 in their explanation that in addition to *Col3a1*, two other genetic factors, *Col1a1* and a cyclic nucleotide phosphodiesterase gene are located on the same chromosome and are thought to together, be possibly relevant to the role of cAMP in the etiology of cleft palate abnormalities (page 5235). Additionally, the reference teaches the implication of the tenascin C gene, an extracellular matrix protein, and several cell-signaling molecules which have been previously implicated in clefting. Diehl et al. further teach the modulation of the clefting phenotype by a non-genetic factor that is a drug exposure and an interaction between two or more non-genetic factors that are drug exposures. The reference reports the findings of a genome-wide search for susceptibility genes for teratogen-induced clefting in the AXB and BXA set of recombinant inbred mouse strains, as they compare the results and the interaction between phenytoin (which induces cleft lip) and 6-aminonicotitinamide (which indices cleft palate) and the cleft palate phenotype (abstract and page 5231). The reference also teaches the method of a non-genetic factors ability to modulate the clefting phenotype wherein the phenotype

is modulated by environmental, non-genetic factors such as a fetus' exposure in utero to ethanol, trimethadione, aminopterin and retinoic acid (page 5231). Included then in these findings are the reference's teachings of the identification of an interaction among two or more non-genetic factors (both environmental and drug-like) and a genetic locus. Furthermore, as stated previously, this same identification was made among multiple genetic loci discovered in this study in addition to those gene mutations that are well known in the art that the present reference reiterates, such as *Msx1*, several *Hox* genes, retinoic acid receptor alpha locus etc, (page 5231).

Response to Arguments:

Applicant's arguments filed July 12, 2006 have been fully considered but they are not persuasive. The examiner would first like to point out that there was not an official rejection made using Mendel's pea plants over the claims of the present invention. Therefore the arguments made regarding Mendel will not be addressed herein.

The applicant's main argument is that the Diehl reference does not state that the RI lines were bred by intercrossing. Specifically Diehl teach that A/J (heterozygous) was crossed with C57BL6/J (heterozygous) to produce the recombinant inbred lines AXB and BXA (which are both homozygous). In order to map the genetic loci that is responsible for clefting the AXB and the BXA lines would have been crossed and their progeny would produce heterozygotes. Applicants also assert that Diehl does not disclose any breeding strategy that produces genetically diverse individuals. However since the individuals produced by crossing AXB and BXA are heterozygotes, then they

are technically genetically diverse with respect to each other. Thus Diehl teaches a renewable population of genetically diverse individuals comprising (See page 5232).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-14, 16-18, and 64-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Diehl et al. in view of Dindzans et al. (J. of Immunology, 1986) and in further view of Hedrich, Hans J. ("Genetic Monitoring, 1981) for reasons set forth in the Office Action of February 10, 2006 and reiterated below.

The teachings of Diehl et al are presented above in paragraph 5.

Diehl et al do not teach the derivation of the RI lines from at least 3, 4 or 8 non-recombinant parent lines or that genetically diverse individuals will be a natural by product from the use of multiple parent strains.

However, Dindzans et al. teach that multiple parents are necessary for the breeding of mice in an attempt to map genes and in the elucidation of mechanisms of genetic control. Dindzans et al. teach "the mode of inheritance of susceptibility/resistance to mouse hepatitis strain 3 (MHV)-3 being determined by typing the set of AXB/BXA recombinant inbred (RI) strain derived from **resistant** A/J and

susceptible C57BL/6J progenitors for susceptibility to infection as determined by the severity of live pathology". "The strain distribution pattern for susceptibility showed a discontinuous variation: one strain was fully resistant (like A/J), four strains were fully susceptible (like C57BL/6J), and 16 strains showed an intermediate degree of susceptibility"(page 2355). Accordingly, it has been suggested that strain-dependent susceptibility to MHV-3 reflects genetically controlled immune defects rather than differences in the non-genetic, in this case viral factor. It is important to note the need for parental strain diversity that the reference teaches as " the AXB/BXA RI strains used in these experiments were derived from susceptible (C57BL/6J) and resistant (A/J) progenitors representing extremes in disease" for the sole purpose of creating RI strains exhibiting distinct patterns of MHV-3 induced liver pathology, and a discontinuous strain distribution pattern of S/R was seen (page 2357, discussion). This reference then teaches the importance of having a "unique assortment of parental genes that are homozygous at every locus, as such strains are useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control"(page 2355). The reference teaches that multiple progenitors were used to establish their population for the expected benefit that using multiple progenitors creates a "unique assortment of parental genes" which is "useful for the mapping of genes and restriction sites and in the elucidation of mechanisms of genetic control".

Dindzans et al. do not teach the derivation of the RI lines from at least 3, 4 or 8 non-recombinant parent lines.

Hedrich teaches the organization of breeding colonies from a founding colony made up of 8-10 breeding pairs. Hedrich teaches in his Chapter on "genetic monitoring" of the mouse in biomedical research, that the organization of breeding colonies should include propagation steps consisting of three groups: "foundation colony (FC), pedigreed expansion colony (PEC), and production colonies (PC)"(Chapter 8, Page 171). Hedrich further teaches that the "foundation colony, which preserves the germline, should be of limited size" and that it may be either be built up as a single line (SL) or in a modified parallel line(MPL) system. With the SL system, Hedrich teaches that "SL colony members are usually more closely related to each other". In contrast, Hedrich teaches that "in the MPL system e.g. three family lines are kept for four generations, each consisting of not more than 8-10 breeding pairs"(Pg. 171). The reference continues to teach that "one breeding pair of the foundation colony is selected as common ancestor, whose offspring will again give rise to three family lines" and further that, "the degree of kinship is varying from generation to generation within the cycle". The reference teaches that this method makes "it possible to select among the lines that one which matches the original standards best".

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl et al. so as to have included the diverse population of non-recombinant, parent lines of Dindzans et al. and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents

would obviously result in a more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best"(Page 171). Therefore, combining the teachings of Diehl et al. in view of Dindzans et al. and in further view of Hedrich would have been obvious at the time the invention was made.

Response to Arguments:

Applicant's arguments filed July 12, 2006 have been fully considered but they are not persuasive.

The applicant's main argument is that Dindzans does not teach using a diverse population of non-recombinant parent lines. However Dindzans does in fact teach that non-recombinant parental lines were used. Specifically Dindzans teaches that the AXB/BXA RI strains were derived from susceptible (C57BL/6J) and resistant (A/J) progenitors. Thus the reference teaches that a diverse population of non-recombinant parent lines were used. Additionally it is argued that Hedrich does nothing to cure the deficiencies of the combined references. However Hedrich's teaching of 8-10 breeding pairs makes obvious the use of at least 3, 4, or 8 non-recombinant parent lines of Dindzans. Applicants also argue that the office misconstrues the meanings of the phrase "genetically diverse". Since the specification does not provide a definition for the term "genetically diverse", it is being given the broadest reasonable interpretation. Additionally it is unclear whether the renewable population in genetically diverse with respect to each other or if it is genetically diverse with respect to other populations.

7. Claims 1-10, 15, 19-27, 46-53, 60-73 and new claims 74 and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipp et al.(Journal of APOA International Vol. 82, No.4, 1999) in view of Mettler et al.(US Patent 6,573,438 B1).

With regard to claim 1, Lipp et al teach a method for identifying a genetic locus that modulates a phenotype, the method comprising:

(a) providing a renewable population of genetically diverse individuals(each different soybean or maize plant), wherein a plurality of the genetically diverse individuals are heterozygous for detectable polymorphism;

(b) mapping the genomes(PCR detection of 2 genetic elements) of individuals within the renewable population of genetically diverse individuals that display the phenotype; and

(c) identifying a genetic locus(35S promoter and the NOS terminator) that modulates the phenotype(insect resistant GMOs) through the mapping step (b).

With regard to claim 3, Lipp et al. teach the above method wherein an individual of the renewable population of genetically diverse individual plants each comprise a diploid organism.

With regard to claim 4, Lipp et al. teach the above method wherein the organism is a plant.

With regard to claim 19, Lipp et al. teach mapping analysis of genetic polymorphisms segregating in the renewable population of genetically diverse individuals such as the many different soy bean and maize plants.

With regard to claims 20 and 21, Lipp et al. teach Roundup Ready® Soybeans that contain in-plant tolerance to Roundup® brand herbicides, enabling growers to spray labeled brands for Roundup® over the top, from emergence throughout flowering, for superior weed control, excellent crop safety and maximum yield potential. Which is to say that that those seeds aren't killed by glyphosate, allowing farmers to spray the weed-killer after planting. In addition, the phenotype of the BT-176 Maize includes insecticidal resistance.

With regard to claims 22-27 and 48-53, Lipp et al. teach the phenotypes above and therein also teach the modulation of said phenotypes by non-genetic factors such as considering the maize plants, the environmental influences of poor weather which affects planting and herbicide use, the amount and type of Lepidoptera larvae that is present, and presence of non-target insect and animals that could all modulate the phenotype of the BT-176 Maize plant. Furthermore, the two or more genetic loci that were identified to modulate the phenotype include the 35S promoter and the NOS terminator that are both important for the expression of genes and are present in nearly all genetically modified plants(Lipp et al. pg 923).

With regard to claim 46, Lipp et al. teach a method for identifying an interaction between a genetic locus(35S promoter and NOS terminator) and a non-genetic factor such as presence of insects, wherein the interaction modulates a phenotype(ability to act as an insecticide) comprising:

a) providing a renewable population of genetically diverse individuals, wherein a plurality of the genetically divers individuals are heterozygous for a detectable polymorphism(the many soybean and maize plants).

b) providing a non-genetic factor to the renewable population(e.g. poor weather)

c) mapping the genomes of individuals that display the phenotype, whereby an interaction between a genetic locus and the non-genetic factor(also can be considered to be contaminating *A. turmefacians* introduced through soil residues on roots see bottom right pg. 924) that modulates a phenotype is identified; and

d) identifying a genetic locus that modulates the phenotype through the mapping and detection of the 35S promoter or NOS terminator.

With regard to claim 60, Lipp et al. teach a method for identifying a genetic locus through PCR amplification of the 35S promoter and the NOS terminator that modulates a phenotype of glyphosate tolerance or insecticide resistance, the method comprising:

a) providing a renewable population of genetically diverse individuals(soy bean and maize plants), wherein the renewable population of plants comprises plants produced by crossing or backcrossing recombinant inbred lines;

b) mapping the genomes(PCR amplifying these 2 genetic elements characteristic of the genome's GMO status) of plants within a reproducible population of diverse plants that display glyphosate tolerance or insecticide resistance; and

c) identifying a genetic locus that modulates the phenotype through the PCR detection step of b).

With regard to new claims 74 and 75, Lipp et al. teach a method for identifying an interaction between a genetic locus and a non-genetic factor, wherein the interaction modulates a phenotype, the method comprising:

a) providing a renewable population(capable of being bred) of genetically diverse(different) produced by crossing or backcrossing different recombinant inbred lines(as every plant is) wherein the renewable population of genetically diverse individuals are heterozygous for a detectable polymorphism(See table 3 for example, overall method not 100% specific and sensitive, heterozygosity present).

b) providing a non-genetic factor to the renewable population(such as those listed above)

c) mapping the genomes of individuals that display the phenotype, whereby an interaction between a genetic locus and the non-genetic factor(also can be considered to be contaminating *A. turmefacians* introduced through soil residues on roots see bottom right pg. 924) that modulates a phenotype is identified; and

d) identifying a genetic locus that modulates the phenotype through the mapping and detection of the 35S promoter or NOS terminator in step c).

Lipp et al.(Journal of APOA International Vol. 82, No.4, 1999) do not teach the method wherein the renewable population of plants are produced by backcrossing recombinant inbred lines comprising less than about 500 lines and further wherein the recombinant inbred lines are derived from at least 3, 4, and 8 different non-recombinant parent lines.

However, Mettler et al.(US Patent 6,573,438 B1) teach these limitations included in claims 2, 8, 9, 11-13, 15-18, 47, and 61-63.

Specifically, with regard to claims 2, 8, 9, 15, and 47 Mettler et al. teach hybrid maize seed produced by crossing plants of an inbred corn line, with plants having a different genotype, and hybrid corn plants produced by growing such hybrid maize seed(Col. 4 lines 44-48).

With regard to claims 11-13, 16-18, 61-63, Mettler et al. also teach that more than 8 recombinant inbred corn lines(e.g. R327H, R372H, R412H, R583H, R660H, 2043 Bt, 2044 Bt, 2070Bt, and 2100Bt) in Col. 4 lines 31-35 can be crossed to provide new hybrid seeds.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Lipp et al. with the method of Mettler et al. since Mettler et al. teach that their genetically modified Btk expression cassette acting similarly as that discussed in the Lipp et al. reference Bt-176, can be transformed "in any plant and particularly corn, wheat, barley, sorghum, and rice plants and more particularly corn plants derived from a transformant or backcrossing through further breeding experiments"(Col. 9 lines 3-6). As such, the Btk expression cassette would also prove to be similarly detected in the method of Lipp et al. in an attempt to decipher the corn's GMO status. Furthermore, the Lipp et al. reference teaches that their method of identifying 2 genetic elements through PCR(35S promoter and NOS terminator) "seems well suited to serve as a screening method to detect the presence of GMOs" especially since "these 2 genetic elements are important

for the expression of genes and are present in nearly all genetically modified plants"(Lipp et al. pg. 923 bottom right).

Response to Arguments:

Applicant's arguments filed July 12, 2006 have been fully considered but they are not persuasive.

The applicant's main argument is that PCR detection is not considered a method of mapping. The specification states that the term "mapping", "genetic mapping", "mapping of the genome", or "genotyping" each refer to a method for describing a position of a genetic locus in terms of recombination frequency with a genetic polymorphism. Furthermore, it is noted that the UC biotech website defines genetic mapping as a determination of the relative locations of genetic information on chromosomes. Therefore Lipps teaching of PCR, meets the limitation of mapping the genome. Applicants further argue that insecticidal resistance is not a phenotype. However if there are 100 ants and they are exposed to insecticide and only 20 survive, they clearly have the phenotype for insecticidal resistance. The applicants also argue that the 35S promoters and the NOS terminator are not genetic loci. However a locus refers to a position on a chromosome and the 35S promoter and the NOS terminator are located at a specific position on the chromosome.

Conclusion

8. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571)

272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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